REMARKS

CLAIM OBJECTIONS - 35 U.S.C. § 132

The Examiner has objected to the amendment filed on November 19, 2002 under 35 U.S.C. § 132 because it introduces new matter into the disclosure. The added material which is not supported by the original disclosure is as follows: the applicant has amended the claims to recite a "non-gene therapy-based method", the specification does not support this term. The Examiner states the Applicant is required to cancel the new matter or specifically point where in the specification support for this terminology can be found.

Applicants have amended the claims to delete the recitation "non-gene therapy-based" from the claims, thereby rendering this objection moot.

CLAIM REJECTIONS - 35 U.S.C. § 112

The Examiner has rejected claims 19-34 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states Applicants' new claims 19-34 introduce new matter into the disclosure of the specification by reciting "non-gene therapy-based" methods.

Applicants have amended claims 19-34 by removing the recitation "non-gene therapy-based" methods from the claims, thus rendering this rejection moot.

The Examiner has maintained the rejection under 35 U.S.C. § 112, first paragraph, for scope of enablement. The Examiner states that the specification, while being enabling for methods of inhibiting the growth of a solid tumor comprising the direct administration to a solid tumor of a xenogeneic retroviral producer cell line which comprises a retrovirus encoding HSVtk

alone or in combination with α (1,3) galactosyltransferase, followed by the administration of gancyclovir, does not reasonably provide enablement for methods of inhibiting tumor growth comprising the administration of any cell containing α (1,3) galactosyltransferase or the administration of any murine cell line followed by any chemotherapeutic agent.

Applicants respectfully traverse this rejection. There is no reason to doubt the disclosure is enabling. It is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement made in a supporting disclosure and to back any assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367, 370 (CCPA 1971)).

> "While the analysis in conclusion of a lack of enablement are based on the [the Wand factors] discusses in MPEP § 2164.01(c) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of the protection sought by the claims. This can be done by making specific findings of fact supported by evidence and then drawing conclusions based on these findings of facts. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case the Examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. However, specific technical reasons are always required. MPEP, Patentability, § 2164.04, 2100-179 (Aug., 2001).

The office action is devoid of any evidence or reasoning which explains why the Patent Office doubts the truth or accuracy of Applicants' description of the invention as defined in the claims. Limitations of coverage to species which have been proved to work or to "preferred" materials, leaves potential avenues for easily circumventing the claims by copiers, and conflicts with the

basic purpose of the patent system. *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976)).

Specifically, the Examiner asserts that the specification does not provide an enabling disclosure for inhibiting tumor growth by the injection/infusion of any type of xenogeneic cells or cells expressing α (1,3) galactosyltransferase to any type of host mammal including humans.

Applicants respectfully traverse. Based on Applicants teachings, any xenogeneic cell will activate the hyperacute rejection since no gene transfer is necessary to the anti-tumor reaction (see spec. pg. 18, lines 28-33). One of ordinary skill in the art would be able to determine which cells other than murine cells are safe and effective as there are many commercial and academic sources of cell lines available (see spec. pg 18, lines 31-33 to pg. 19, linc 1). Additionally, one of ordinary skill would be able to develop cells lines to use in the present invention. (See spec. page 18, 28-33 to page 19, lines 1-3).

The Examiner asserts the specification fails to disclose any means for inducing hyperacute rejection other than the introduction of murine vector producer cell lines which express a retrovirus encoding a gene such as HSVtk or α (1,3) galactosyltransferase to humans.

Applicants respectfully traverse. The specification discloses on page 8 starting at line 22 that "Strong immunological barriers to xenotransplants can destroy a transplant solid organ within minutes, a process termed hyperacute rejection. This hyperacute rejection model of xenograft survival is typically a vascularized rejection model directly exposed to blood serum." Thus, Applicants disclose than another means for inducing a hyperacute rejection is via xenotransplants involving the vascular system of an organ.

Additionally, the Examiner asserts the specification fails to provide sufficient guidance as to the level of expression of α (1,3) galactosyltransferase or the level of complement activation

required to induce hyperacute immune responses *in vivo* and further to produce a therapeutic immune or innocent bystander effect on local tumor cells.

Applicants respectfully traverse. Starting on page 17, line 30 of the specification, Applicants disclose in the Examples dosages of xenogeneic cells given. (See spec. page 18, lines 1-3). Moreover, one of ordinary skill would be able to determine a dose level appropriate for the tumor and the patient which is both safe and effective. (See spec. page 19, lines 10-13).

Further, the Examiner asserts neither the art nor the specification provides any evidence that the destruction of the xenogeneic cell or xenogeneic viral producer cells *in vivo* results in any observed tumor treatment in the absence of tk/ganciclovir therapy.

Applicants traverse. The phase I data as disclosed in the specification was designed to determine if anti-tumor responses observed in earlier trials, often attributed by other investigators, such as Klatzmann, to HSVtk enzyme activation of GCV was correct. The current paradigm theorizes that the HSVtk gene activation leads to a bystander effect that accounts for the observed anti-tumor response. (See spec. pg. 20, lines 15-20). Starting on page 21, in Example 2, Applicants disclose that in the phase I clinical trial four of ten evaluable patients demonstrated some evidence of an anti-tumor response employing Applicants' method. On page 27, for example, shows one patient had the complete resolution of a mass and 70% reduction on CA125. Of the remaining three, one had a partial, the second had a minor, and the third showed a mixed response. The patient with the mixed response demonstrated significant resolution of malignant ascites prior to GCV infusion even though the patient developed a malignant pleural effusion. Figure 1 shows the results of PCR analysis of peritoneal washes and biopsies conducted on patient 4. (Spec. page 27, lines 17-19). Moreover, Applicants point out that the

demonstration of tumor regression with only low level gene transfer (<1%) suggests that hyperacute rejection of the murine cells might inhibit the cancer by innocent bystander effect. Additionally, in Example 6, starting on page 29, Applicants disclose that no HSVtk gene transfer into peripheral blood lymphocytes (PBL) from patient blood samples up to 3 months after vector producer cell infusion was detected by PCR in any patient. (See spec pages 29-30). Moreover, Example 12, starting on page 35 of the specification, demonstrates that presentation of αgal alone on human tumor cells induces sensitivity to human serum.

The Examiner also asserts the specification does not provide any guidance as to the selection of chemotherapeutic agents, or for dosages, routes of administration, or timing between the administration of the murine cells and the chemotherapeutic agent.

Applicants respectfully traverse. Applicants state in the specification on page 19 that one of ordinary skill in the art would be able to determine additional treatments which would work subsequent to the present treatment. Applicants respectfully submit that the specification need not disclose what is well known in the art.

Claims 19-34 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner states new claims 19-34 recite a "non-gene therapy-based method" for inhibiting tumor growth. The specification does not recite the phrase "non-gene therapy-based" or provide a definition of the "non-gene therapy-based" method.

Applicants have deleted the recitation "non-gene therapy-based method" from the claims, thus rendering this rejection moot.

DOUBLE PATENTING

The Examiner states new claims 19-24 and 26-29 remain unpatentable over claims 4 and 7 of U.S. Patent 5,869,035, hereafter referred to as the '035 Patent. The Examiner states it is

noted that the Applicants stated in the response submitted on June 18, 2002 that a Terminal Disclaimer over U.S. Patent 5,869,035 was submitted to the Office. However a Terminal Disclaimer over U.S. Patent 035 has never been received. If Applicants have in fact submitted such a document, the Office requested a copy be provided for entry into the instant record. In view of the fact that a Terminal Disclaimer is not of record in the instant case, the double patenting rejection in concurrent rejection of the claims under 35 U.S.C. § 102(e) has been maintained.

Applicants are herein submitting a copy of the Terminal Disclaimer previously filed on April 3, 2002. Applicants respectfully request that this copy be entered into the instant record.

CLAIMS REJECTIONS - 35 U.S.C. § 102

The Examiner states that as noted above, the Terminal Disclaimer referred to by the Applicants has not been received by the Office. As such, it cannot be relied on to overcome the instant grounds of rejection under 35 U.S.C. § 102(e).

Applicants are herein submitting as stated above, a Terminal Disclaimer to overcome the instant grounds of rejection under 35 U.S.C. § 102(e). Applicants respectfully request that this rejection be withdrawn with the submission of this Terminal Disclaimer.

The Examiner has rejected new claims 19-34 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,045,789, hereafter referred to as Culver.

The Examiner states Culver teaches the injection of a murine retroviral packaging cell line which produces a retrovirus encoding HSVtk to a solid tumor in a subject resulting in tumor treatment following ganciclovir administration (Culver, column 13, lines 39-57 and column 14, lines 1-14, and claims 1-5). Culver teaches that the intended subject for the disclosed method is a human cancer patient. Culver further teaches that the administration of the murine HSVtk

retrovirus producing cell to the tumor resulting in bystander killing of tumor cells which do not express HSVtk. (See for instance column 4). The Examiner states that while Culver does not explicitly teach that the murine cells express α (1,3) galactosyl epitopes, it is an inherent property of murine cells that they utilize α (1,3) galactosyltransferase in protein glycosylation and that murine proteins contain α (1,3) galactosyl epitopes. In addition, Culver teaches that the disclosed method is useful for treating a number of solid tumors including ovarian tumors (see column 10, lines 13-21). Thus, Culver teaches the treatment of tumors comprising the administration of xenogeneic murine retrovirus producing cells directly to a tumor in a subject which includes humans wherein the murine cells produce a retrovirus which encodes HSVtk and IL-2 such that an immune response is generated against the tumor and that tumor cells are also killed directly by HSVtk/ganciclovir or indirectly by innocent bystander effect. By teaching all the limitations of the claims, Culver anticipates the instant invention as claimed.

Applicants have amended claims 19, 26, and 32 to recite activation of a hyperacute rejection. Applicants submit Culver does not anticipate because Culver fails to teach the limitation of activating a hyperacute rejection in human tumor cells that are infused with murine producer cells. Culver merely teaches a method of treating a tumor by initially identifying the tumor as one displaying a "bystander effect" whereby the transfer of a gene conferring sensitivity to a chemotherapeutic agent. Moreover, while Culver may intend the subject to be human, all the examples use mice as subjects.

On the contrary, Applicants' method is an immuno-therapy based method because the therapeutic effect is achieved by the activation of a hyperacute rejection by the delivery of retroviruses that provide the production of retroviral vectors within the solid tumor. Thus, tumor destruction is achieved by introducing murine cells prior to gene transfer and in the absence of

the administration of ganciclovir. Applicants have shown an anti-tumor response is seen upon the activation of the hyperacute rejection. The results seen in the ovarian cancer phase II trial submitted herein by Declaration of Dr. Charles J. Link Jr., rule out the mechanism of tumor cancer killing mediated by gene transfer of thymidine kinase and gancyclovir. Increase in anti-α Gal antibodies in serum, increase in C3 complement levels, and *in vitro* killing of murine cells mediated by patient's sera and peritoneal wash fluid suggests an anti-tumor mechanism mediated by anti-α Gal antibodies and complement mediated destruction of the xenogeneic cells, i.e., murine vector producing cells (VPC), which leads to a bystander immune reaction against the tumor cells. Thus, Culver fails anticipate because he does not contemplate or disclose the limitation of a hyperacute rejection.

The Examiner also states that since Culver teaches that the murine cells express α (1,3) galactosyl epitopes, it is an inherent property of murine cells that they utilize α (1,3) galactosyltransferase in protein glycosylation and that murine proteins contain α (1,3) galactosyl epitopes.

Applicants respectfully traverse. Culver does not anticipate under inherency. Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. Culver does not necessarily function in accordance with the claimed limitations of inducing a hyperacute rejection. Culver uses mice as subjects. While the enzyme α (1,3) galactosyltransferase is expressed in a variety of mammalian species including *mus musculus*, or mouse, it is not expressed in humans due to the presence of two base frameshift mutations. Thus, if the mouse is αgal+, hyperacute rejection will not contribute to the observed immune response. However, a human, as disclosed by Applicants is different. Applicants have found that the retroviral transduction of human tumor cells with the α (1,3) galactosyltransferase

gene resulted in expression (see spec. pg. 11, lines 31-32). These human cells displayed αgal and became sensitive to human serum (see spec pg. 11, line 32 to pg. 12, lines 1-2). Applicants claim that upon the delivery of the vector producing cells to the tumor, antibodies and complement-mediated hyperacute rejection against the murine cells occurs. (See claims 19, 26, and 32). So, the teachings of Culver do not necessarily function in accordance with the limitation of administration of murine retroviral vector producer cells expressing the α (1,3) GT gene into human tumor cells which create epitopes that activate hyperacute rejection which would not normally be found in αgal+ mice. Applicants respectfully request the Examiner for reconsideration.

The Examiner has rejected claims 19-24 and 26-29 under 35 102(a) over Klatzmann et al. The Examiner states Klatzmann teaches the treatment of melanoma tumors in humans by direct intratumoral injection of a xenogeneic murine retroviral producing cell line that produces a retrovirus encoding HSVtk followed by the administration of ganciclovir (GCV). Further, while Klatzmann does not explicitly teach that murine retroviral producer cells express α (1,3) galactosyl epitopes, it is an inherent property of murine cells that they utilize α (1,3) galactosyltransferase in protein glycosylation and that murine proteins contain α (1,3) galactosyl epitopes. Klatzmann observed local inflammatory reactions at the tumor site following the injection of the xenogeneic cells and specifically states that the transplanted murine cells are rejected within 7-10 days as a result of hyperacute rejection mediated by preformed antixenogeneic antibodies and complement (Klatzmann, page 2585, abstract). Thus, the Examiner states it would appear the ability of xenogeneic murine retroviral producer cells which produce a retrovirus encoding HSVtk to generate hyperacute immune responses in a human which result in innocent bystander killing of tumor cells is an inherent property of the xenogeneic

murine retroviral producer cells. Thus, by teaching all the limitations of the instant methods, Klatzmann anticipates the invention as claimed.

Applicants have amended claims 19-24 and 26-29 to more clearly recite the claimed invention. Applicants respectfully submit that Klatzmann discloses a suicide gene therapy method based on retrovirus-mediated gene transfer of herpes simplex virus type 1 thymidine kinase (HSV-1 tk), which specifically sensitizes dividing cells to GCV toxicity. Klatzmann's method of tumor destruction is attributed to the anti-tumor response of GCV being activated by the HSVtk enzyme. Klatzmann merely asserts side effects of therapy consisting chiefly of local inflammatory reactions or fever when multiple injections are administered. Klatzmann characterizes the inflammatory skin reactions at injection sites as consisting of local erythena or redness to the skin due to capillary dilatation with edema or the accumulation of an excessive amount of watery fluid and cells. (See page 2587 column 2, under "Clinical data" to pg. 2589, column 1, lines 1-3). Moreover, Klatzmann utilizes suicide gene therapy directed at superficial lesions (see page. 2593 col. 1, 2nd para.) wherein the packaging cells are directly injected into the tumor in order have gene transfection.

Conversely, Applicants' invention is an immunotherapy-based method, which involves the activation of the immune response against a metastatic tumor by administering murine VPC proximal or distal to the tumor in the peritoneal cavity of the subject. The vector producing cells induce a hyperacute rejection without activation of a HSVtk gene as described by Klatzmann. Applicants' method of tumor destruction is attributed to the activation of a hyperacute rejection by the delivery of retroviruses that express αgal to the vicinity of the tumor, therefore causing the tumor to become sensitive to human serum. It is particularly important to note that this tumor destruction is achieved by the administration of murine cells in the absence of gene transfection

and no administration/infusion of GCV. Applicants respectfully submit that the hyperacute rejection may cause a strong intraperitoneal inflammatory response that through a bystander mechanism destroys cancer cells (see spec. pg. 12, lines 7-9). Thus, Applicants respectfully submit that the mere fact that Klatzmann teaches use of the murine cells is not sufficient to show the effect of a hyperacute rejection against the tumor and subsequent induction of an immune reaction in the absence of the activation of the HSVtk gene by the infusion of ganciclovir because Klatzmann teaches a method of killing the tumor based on HSVtk gene transfer followed by the activation of this suicide gene by the infusion of GCV.

A person of ordinary skill in the art would not recognize that the administration of α (1,3) galactosyl-containing cells would activate a hyperacute rejection response against a tumor cell and the induction of an immune response in the absence of gene transfer and infusion of GCV. Klatzmann certainly does not recognize this because as stated above the destruction of the tumor is attributed to the activation of the HSVtk gene by the infusion of GCV. Therefore, Klatzmann does not anticipate under the principle of inherency.

While not expressly addressed by the Examiner, Applicants respectfully submit that Klatzmann would not be obvious to one of ordinary skill in the art. The fact that Applicants use the administration of murine vector producing cells to induce a hyperacute rejection against the tumor itself, despite the expectation in the art that HSVtk and GCV gene therapy is efficacious for the treatment of solid tumors in adults, is strong evidence of unobviousness.

Moreover, Klatzmann teaches away or goes off in a different direction than that of the claimed invention because Klatzmann teaches that "in regard to immune-mediated destruction of packaging cells, it may be possible to significantly improve their survival", for example, by "humanizing" the murine cells or using intravenous immunoglobulins (see pg. 2593, col. 1, first

full para.). This is clearly divergent to the claimed invention which teaches that the anti-tumor response is due to a hyperacute rejection associated with the administration of murine VPC which has a rapid adverse effect on the tumor in the peritoneal cavity.

Please charge Deposit Account No. 26-0084 the amount of $135.00 for the cost of extra independent claims (new claims 35, 36, and 39; $126.00) and an extra claim over twenty ($9.00).

In addition, please charge Deposit Account No. 26-0084 the amount of $205.00 for a two-month extension of time.

No other fees are believed to be due in connection with this amendment; however, consider this a request for any inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	LINK et al.
SERIAL NO	:	09/589,255
FILED	:	June 7, 2000
TITLE	:	METHOD FOR TUMOR TREATMENT USING INFUSION OF XENOGENEIC CELLS TO INDUCE HYPERACUTE REJECTION AND INNOCENT BYSTANDER EFFECT
Grp./A.U.	:	1632
Examiner	:	WEHBE, Anne Marie Sabrina
Conf. No.	:	8671
Docket No.	:	P04091US1

DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Charles J. Link Jr., declare the following:

1. That I am an inventor in the above-identified patent application;

2. That I graduated in 1982 with a Bachelor of Arts degree from the Leland Stanford Junior University and in 1985 with a medical degree from the Stanford University School of Medicine, Stanford, California;

3. That I have been working in the field of cancer research since about 1982;

4. That I am familiar with the above-identified patent application and with the references cited by the Examiner, i.e., the Culver Patent U.S. Patent No. 6,045,789 and Klatzmann et al. reference, "A Phase I/II Dose Escalation Study of Herpes Simplex Virus Type 1 Thymidine Kinase 'Suicide' Gene Therapy for Metastatic Melanoma," *Human Gene Therapy* 9: 2585-2594 (November 20, 1998);

5. That an Ovarian Cancer Phase II Trial was performed under my direction with the following protocol schematics:

Day -30 to -1:	Patients found to be eligible for protocol.
Day -7 to -1:	Laparotomy or laparoscopy with tumor biopsy. Surgery may include tumor debulking and/or the lysis of adhesions. Placement of peritoneal dialysis catheter.
Day 0: Cycle 1:	Injection of LTKOSN.1 vector producer cells.
Day 7 and 14:	Peritoneal washing: evaluate nature of immune response and look for HSV-TK positive tumor cells.
Day 27:	Evaluate for response: determination of anti-tumor efficacy before the initiation of GCV treatment by laparoscopy and/or CT scan and determination of the marker CA125 levels in serum.
Day 28-41:	Treatment with prodrug GCV (5 mg/kg, b.i.d.).

Abbreivations: HSV-TK = herpes simplex virus thymidine kinase; GCV = gancyclovir; bid = L. *bis in die*, twice a day

Day 48:	Evaluate for response. Determination of anti-tumor efficacy from GCV by laparoscopy and/or CT scan and CA125.

6. That if a patient showed progressive disease after cycle 1, the patient was off the study. If patient showed stable or responsive disease, the study proceeded to cycle 2;

7. That preliminary ongoing results of Ovarian Cancer Trial, Phase II study of Patient #1 consisted of the following:

a. Anti-alpha Gal Antibodies:

Cycle1: On days 14 and 28 serum was collected and anti-alpha Gal antibody (Ab) titers were determined, showing a 128-fold increase over baseline levels.

Cycle 2: On day -1 of cycle 2, Ab titers were increased 32 fold over day 0 (day 0 is the first day of Cycle 1).
On days 14 and 28 of the second cycle, anti-alpha Gal specific Ab showed a 128-fold increase over the levels of day 0.

Cycle 3: On day -1 of cycle 2, Ab titers were increased 32 fold over day 0 (day 0 is the first day of Cycle 1).
On days 14 and 28 of the second cycle, anti-alpha Gal specific Ab showed a 128-fold increase over the levels of day 0;

8. That this patient did not develop any significant antibodies anti-FBS (fetal bovine serum);

9. That the serum IgG and IgM content did not change and were similar to the baseline values;

10. That IgG content in peritoneal washes was not done due to the lack of material;

11. That complement C3 and C4 determination were as follows:

C3 Levels

Day	Cycle 1	Cycle 2	Cycle 3
0	154	148	161
7	230 (high)	222 (high)	208 (high)
14	211 (high)	153	189
28	130	141	140

C4 values were between 27.8 and 37.7 during all three cycles;

12. That killing of murine cells by patient's sera consisted of a baseline sample containing 90% of serum and 10% DMEM (Dulbecco's Modified Eagle Medium) killed 77% of mouse cells (LTKOSN.1 VPC) *in vitro*. All samples of sera after that achieved 100% killing.

Tests were performed on days 14 and 28 of Cycle 1; days -1, 14 and 28 of Cycle 2 and on days 0, 14 and 28 of Cycle 3;

13. That killing of murine cells by peritoneal wash fluid consisted of a baseline sample containing 90% of peritoneal wash fluid and 10% DMEM killed 5% of mouse cells *in vitro*. After that, the fluid displayed 91% cell killing at day 14 of Cycle 1; 46% killing on day 1 of Cycle 2 and 93% of killing on day 14 of Cycle 2;

14. That according to clinical observations, the patient achieved stable disease by CT scan by day 28 of cycle 1 (before any gancyclovir (GCV) infusion) compared to a pretreatment scan;

15. That for detection of gene transfer, PCR for tk and env gene from tumor biopsies were all negative and PCR for tk and env gene from peritoneal washes were positive at days 7 and 14 of each cycle and negative at day 28 of each cycle;

16. That in summary, these results indicate that stable disease was achieved by intraperitoneal infusion of murine cells, in the absence of gene transfer and before the administration of GCV. These results rule out the mechanism of tumor cell killing mediated by gene transfer of thymidine kinase and gancyclovir. Increase in anti-alpha Gal antibodies in serum, increase in C3 complement levels and *in vitro* killing of murine cells mediated by patients sera and peritoneal wash fluid suggest an anti-tumor mechanism mediated by anti-alpha gal antibodies and complement mediated destruction of xenogeneic cells, which leads to a bystander immune reaction against the tumor cells.

17. That the undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

Date: June 24 2003

Charles J. Link Jr. M.D.